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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/259,658	02/26/1999	JOHN COLYER	04256/79245	5554

29933 7590 05/12/2006

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 05/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/259,658	COLYER ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/9/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,18,21-38 and 41-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *42-45* is/are allowed.

6)☒ Claim(s) *17,18,21-31,34-38 and 41* is/are rejected.

7)☒ Claim(s) *32 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 17-18,21-38 and 41 and new claims 42-45 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Claim Objections/Rejections - 35 USC § 112

1. ***Withdrawn Claim Objections*** Amended Claim 24 objected to because of the following informalities has been obviated by amending the claim through deleting the first recitation of "labeled". ***Claim***

2. ***Withdrawn Rejections - 35 USC § 112*** Amended claim 21 no longer recites the limitation "test sample" in reference to the term "sample".

Allowable Subject Matter:

3. Claims 42-45 define over the prior art of record.

4. Claims 32-33 remain objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Response to Arguments

5. Applicant's arguments filed January 5, 2006 have been fully considered but they are not persuasive.

6. **(Maintained)** The rejection of claim 17 under 35 U.S.C. 102(b) as being anticipated by Fitzpatrick et al (US Pat. 5,710,009) was traversed on the grounds that: each and every limitation of the claim must be disclosed by the prior art reference.

7. It is the position of the examiner that Fitzpatrick et al disclose and claim a composition that comprises receptor, reland and a means for detection of released reland or receptor (when it is desired to detect released receptor).

Support—Reland(1st polypeptide):receptor complex (2nd polypeptide, antibody that binds to the 1st polypeptide).

8. The immobilized complex comprises:

- a polypeptide pair (receptor-release ligand complex(see claim 19)) the two polypeptide complex being immobilized on a support (see claim 18, "solid support"; claim 19, "membrane" support)
- the **first polypeptide** is referred to as a reland (see peptide reland, col. 5, lines 4-6 and 22). The term "reland" is a term defined by Fitzpatrick to mean:

9. reland is a term coined by the co-inventors hereof to refer to a release ligand. The release ligand or reland binds with the receptor with a low association constant, and does not affect the stability of an analyte:receptor complex. Thus, a reland is structurally related to its cognate analyte to allow for a specific binding interaction, but also includes sufficient structural differences to lower affinity and to preclude formation of irreversibly bound complexes. Accordingly, a reland may be an analog of the analyte, including an epitope of the analyte, a derivative of the analyte, a modified analyte, or an isomer of the analyte. Preferably, the reland differs structurally from analyte in a location at or near the epitope. These differences may include chemical modifications, steric, configurational, conformational, or ionic changes. Preferably, ionic groups are substituted with a neutral polar groups, since ionic interactions are particularly strong, and may interfere with release. (col. 5, lines 4-6, line 22)

The **second polypeptide** (see receptor, col. 5, lines 54-60) being an antibody, which is referred to by Fitzpatrick as a receptor that binds to the first polypeptide. The first polypeptide is immobilized on the solid support and complexed with the second polypeptide (see claim 19, kit composition claim), but modification of the first polypeptide by glycosylation would modify binding between the first and second polypeptides (see entire narrative of Example 3 of Fitzpatrick et al).

10. Applicant asserts that none of the polypeptides of Fitzpatrick et al are covalently modified as required by instant claim 17.

11. It is the position of the examiner that the functional *methods step* claim limitations recited in the **composition** of instant claim 17 functionally define *capabilities* that must be possible at some *future time* when the polypeptide pair is incorporated into an assay method or process.

- The claimed invention requires the polypeptide pair to be immobilized on a support; Fitzpatrick et al discloses this composition (see above, claim 19).
- The claimed invention requires the polypeptide pair to be detectable; Fitzpatrick et al detects the complex with an antibody to a member of the polypeptide pair (see Example 3, Fitzpatrick et al).
- The claimed invention requires one of the polypeptides to be covalently modifiable by glycosylation, which modification of one of the polypeptides modifies the binding of the two polypeptides. These claim limitations are disclosed by Fitzpatrick et al in that the antibody binds to the glycosylated form of the polypeptide with greater affinity, that the deglycosylated form, thus if the reland were to be glycosylated (covalently modified with a sugar group), the binding of the antibody (second polypeptide) to the first polypeptide (covalently modified with glucose), would be increased binding affinity (see Example 3, col. 27of Fitzpatrick et al).

The disclosure of Fitzpatrick et al describes a deglycoslyated hemoglobin and an antibody complex that is on a support, wherein the antibody will also bind with modified binding affinity, specifically greater binding affinity, to covalently modified/glycosylated hemoglobin ('009, col. 10, lines 61-65; col. 27, Example 3 and claim 19).

12. Applicant further asserts that claim 17, must be covalently modified.

13. It is the position of the examiner that the hemoglobin was deglycosylated to obtained the immobilized complex of the first polypeptide with the second polypeptide. Additionally, the combination of claim limitations recited in claim 17 are conditional claim limitations (i.e. "is detectable", and need not be detectably labeled but must be able to be detected. Claim 17 also recites "and covalent modification of at least one of the polypeptides results in modulation"; this is a future tense event defined by "results in". The polypeptide pair need not be covalently modified in order to bind to each other . Claim 17 lists possible modifications, based upon the recited claim limitations that *can take place in the future.*

14. Applicant's traversal is not commensurate in scope with the instantly claimed invention as now claimed. Clearly the immobilized first polypeptide (reland) can be modified by glycosylation, in light of the fact that Fitzpatrick et al showed the glycosylated polypeptide to evidence a higher binding affinity to the antibody than the unglycosylated form of the polypeptide. The rejection is maintained for reasons of record and responses set forth above.

15. **(Maintained)** The rejection of (composition) claim 17 under 35 U.S.C. 102(b) as being anticipated by Hochstrasser et al (US Pat. 5,565,352) is traversed on the grounds that "neither of the anti-ubiquitin antibody or the immobilized ubiquitin-oligo peptide are "covalently modified" as required by claim 17.

16. It is the position of the examiner that claim 17 does not recite the phrase: covalently modified as asserted by Applicant.

17. The combination of claim limitations recited in claim 17 are conditional claim limitations, specifically "is detectable", and need not be detectably labeled but must be able to be detected.

18. Claim 17 also recites "and covalent modification of at least one of the polypeptides results in modulation"; this is a future tense event defined by "results in".

19. The polypeptide pair is the combination of a first polypeptide being an ubiquitin-oligopeptide covalent conjugate complexed with a second polypeptide being an anti-ubiquitin antibody polypeptide. (see col. 1, lines 23-25, and lines 26-45) and each polypeptide need not covalently modify each other.

20. Claim 17 lists possible modifications, based upon the recited claim limitations that can take place in the future that must be able to modify binding. Applicant's traversal is not commensurate in scope with the instantly claimed invention as now claimed. The rejection is maintained for reasons of record and responses set forth above.

21. (**Maintained**) The rejection of (method) claims 18, 21-26,31, and 34-38 under 35 U.S.C. 102(b) as being anticipated by Hochstrasser et al (US Pat. 5,565,352) is traversed on the grounds that the claims require the presence of a first polypeptide, a second polypeptide, a modifying enzyme and a modifying group substrate, distinct elements and Hoschstrasser et al does not disclose the combination of all of the elements.

22. It is the position of the examiner that Hoshstrsser et al disclose the instantly claimed methods that comprise the steps of:

providing a first and second polypeptides (protein (short lived proteins/polypeptides, col. 33, lines 30-43) substrate (col. 26, line 29) and deubiquitinin enzyme (see title and entire document)), wherein one of the polypeptides is immobilized (see col. 26, lines 66-67 through to col. 27, lines 1-5), and at least one of the polypeptides is

- susceptible to covalent modification (see col. 28, line 49 "covalently modifies enzyme" polypeptide / the substrate polypeptide that is modifiable by ubiquinin (see

col. 33, lines 29-32 by covalent modification) or glycosylation or prenylation (see col. 26 and 33);

providing a modifying group substrate (see col. 33, lines 29-31 and col. 26, lines 32-33)

allowing the polypeptides to bind to each other (base line activity (see col. 27, lines 18-21, measuring the association of the first and second polypeptides by contacting the);

contacting the polypeptides with a modification enzyme (ie E2 enzyme ubiquinate or other modifying enzyme that will glycosylate or prenylate a substrate) in the presence of said modifying group substrate (modifying group is a polyubiquitin or ubiquitin or prenyl- or glycosyl- modifying group substrate)

detecting modulation of the binding of the polypeptide(base line activity (see col. 27, lines 18 and see Figure 6) which determines covalent modifications of the polypeptides in the presence of a modifying enzyme to determine a reference signal

contacting the polypeptides with a modification enzyme and a candidate modulator (see col. 26, lines 13-18), col. 27, lines 18-27, lines 33-47);

detecting modulation of binding of the polypeptides in the presence of the candidate modulator (see col. 28, lines 24-39, and 41-59) and

comparing the modulation detected in the presence of the candidate modulator with the baseline reference signal modulation (see col. 26, lines 13-18, modifying or inhibiting activity; stimulation or inhibition of activity, see col. 34, lines 63-69; relative to a control (see col. 28, lines 60-67).

- an assay of a polypeptide substrate modified by polyubiquitin, which is

proteolytically digested and further modified by the disclosed deubiquitination enzyme (see Figure 6b). Relative levels of activity relative to type of substrate covalent modifications were determined through comparison relative to a reference control value in the Examples.

23. The assay for agonists/antagonists/modulators (see col. 25, lines 30-51) of activity are disclosed to include a candidate substance (see col. 26, lines 13-15) which are combined with the first polypeptide, a substrate second polypeptide/protein, co-factors, relevant modifications such as glycosylation or prenylation.

24. Among the disclosed **second polypeptide** are "short-lived eukaryotic proteins,

Among the defined polypeptides that are short lived proteins are:

cyclins, c-mos protein kinase ; MATα2 (see col. 33, lines 30-43). The modifying enzyme which attaches ubiquitin to the substrate protein/polypeptide is E2 enzymes (see col. 33, lines 53-59).

With respect to assaying biological samples and detecting modifying enzymes in the sample, Hochstrasser et al discloses the following:

The present invention provides a process of screening a **biological sample** for the presence of an deubiquitinating enzyme polypeptide. A biological sample to be screened can be a biological fluid such as extracellular or intracellular fluid or a cell or tissue extract or homogenate. A biological sample can also be an isolated cell (e.g., in culture) or a collection of cells such as in a tissue sample or histology sample. A tissue sample can be suspended in a liquid medium or fixed onto a solid support such as a microscope slide

Ubiquitin-dependent proteolytic substrates require attachment of an **isopeptide-linked multiubiquitin** chain for efficient degradation (Chau, 1989).

Ubiquitin is a 76 amino acid residue protein that is either free or covalently joined, through its carboxyl-terminal glycine residue, to various cytoplasmic, nuclear, and integral membrane proteins. The attachment of ubiquitin to proteins is catalyzed by **ubiquitin-conjugating enzymes (also called E2 enzymes)**. Ubiquitin is conserved among eukaryotes to an extent unparalleled among known proteins.

The ability of Doa4 to deubiquitinate a protein with ubiquitin in isopeptide linkage was tested with a ubiquitin-Lys48-ubiquitin dimer (Cook et al., 1992) as substrate, in which the a-carboxyl group of one ubiquitin is attached to the e-amino group of Lys48 in the second ubiquitin (the same linkage found in the multiubiquitin chains formed on proteolytic substrates (Chau, 1989)).

Assays of Ub, cleavage were done with GST-Doa4 or GST-tre-2 proteins partially purified from E. coli JM101 (Ausubel et al., 1989). Equal amounts of protein were incubated at 37.degree. C. with 60 ng of Ub.sub.2.sup.22 in 50 mM Tris-HCl (pH 7.6), 4 mM DTT. Proteins were detected by anti-ubiquitin (East Acres Biologicals) immunoblot analysis with the ECL system (Amersham). bgal activity was measured as described (Hochstrasser & Varshavsky, 1990).

Detailed Description Text (204):
To gain insight into the mechanistic role(s) of the Doa4 enzyme in ubiquitin-dependent proteolysis, we examined intracellular ubiquitin and ubiquitin-protein conjugates by anti-ubiquitin immunoblot analysis (FIG. 6a). Exponentially growing cells in minimal media (10 ml) were harvested by centrifugation. Cells were disrupted by incubation in 50 ml of SDS loading buffer (Ausubel et al., 1989) at 100.degree. C. for 10 min. Debris was cleared by centrifugation. .about.10% of each supernatant (volumes were normalized to cell densities) was run on an 18% SDS-polyacrylamide gel; proteins were blotted onto PVDF. Ubiquitin-containing proteins were detected with an antiubiquitin antibody (East Acres Biologicals) and the ECL system. The indicated ubiquitin-containing species were also observed with an independent anti-ubiquitin antiserum (Deveraux et al., 1990). The two proteins marked by asterisks did not react with this antiserum.

screening assays for the testing of candidate substances are designed to allow the investigation of structure activity relationships of other molecules with the enzyme, e.g., study of binding of naturally occurring hormones or other substances capable of **interacting or otherwise modulating with the enzyme versus studies of the activity caused by the binding of such molecules to the enzyme.** In certain embodiments, the polypeptides of the invention are crystallized in order to carry out x-ray crystallographic studies as a means of evaluating interactions with candidate substances or other molecules with the deubiquitinating enzyme polypeptide. For instance, the purified recombinant polypeptides of the invention, when crystallized in a suitable form, are amenable to detection of intra-molecular interactions by x-ray crystallography

Detailed Description Text (131):
For example, if an agent can bind to the enzyme of the present invention, the binding can be detected by using radiolabelled agent or radiolabelled enzyme. Briefly, if radiolabelled agent or radiolabelled enzyme is utilized, the **agent-enzyme complex** can be detected by liquid scintillation or by exposure to X-Ray film.

Detailed Description Text (132):
When **an agent modifies the enzyme**, the modified enzyme can be detected by differences in mobility between the **modified enzyme and the unmodified enzyme** through the use of chromatography, electrophoresis or centrifugation. When the technique utilized is centrifugation, the differences in mobility is known as the sedimentation coefficient. The modification can also be detected by differences between the spectroscopic properties of the modified and unmodified enzyme. As a specific example, if **an agent covalently modifies a enzyme**, the difference in retention times between modified and unmodified enzyme on a high pressure liquid chromatography (HPLC) column can easily be detected.

Detailed Description Text (139):
In accordance with a screening assay process, a biological sample is exposed to an antibody immunoreactive with the deubiquitinating enzyme polypeptide whose presence is being assayed. Typically, exposure is accomplished by forming an admixture in a liquid medium that contains both the antibody and the candidate deubiquitinating enzyme polypeptide. Either the antibody or the sample with the deubiquitinating enzyme polypeptide can be affixed to a solid support (e.g., a column or a microtiter plate).

Detailed Description Text (140):
The biological sample is exposed to the antibody under biological reaction conditions and for a

period of time sufficient for antibody-polypeptide conjugate formation. Biological reaction conditions include ionic composition and concentration, temperature, pH and the like.

Detailed Description Text (142):
Exposure time will vary inter alia with the biological conditions used, the concentration of antibody and polypeptide and the nature of the sample (e.g., fluid or tissue sample). Means for determining exposure time are well known to one of ordinary skill in the art. Typically, where the sample is fluid and the concentration of polypeptide in that sample is about 10.sup.-10 M, exposure time is from about 10 minutes to about 200 minutes.
Detailed Description Text (143):
The presence of deubiquitinating enzyme polypeptide in the sample is detected by detecting the formation and presence of antibody-deubiquitinating enzyme polypeptide conjugates. Means for detecting such antibody-antigen (e.g., enzyme polypeptide) conjugates or complexes are well known in the art and include such procedures as centrifugation, affinity chromatography and the like, binding of a secondary antibody to the antibody-candidate enzyme complex.

FP*	SP*	MGS*	modifying*
Enzyme (col. 26,l. 28-29)	protein substrate (c.26,l.29)	glycosylation	glycosylating E (c. 26,l.32-33)
Enzyme(c. 26, l.28-29)	protein substrate (c.26,l.29)	prenylation	prenylating E (c. 26,l. 32-33)
Enzyme	Short lived protein substrate polypeptide	Ubiquination	E2 enzyme (c.33,l. 58)

l.:line c or col.:column E. enzyme FP: immobilized first polypeptide

SP: second polypeptide MGS: modifying group substrate Modifying: modifying agent

25. ***Rejection Maintained Claim Rejections - 35 USC § 102***: The rejection of claims 17 and 41 under 35 U.S.C. 102(b) as being anticipated by Avruch et al (US Pat. 5,582,995) in light of Avruch et al (US Pat. 5,736,337) who provides evidence that Ras/Raf binding is effected by phosphorylation, and dephosphorylation (see '337, col. 20, lines 1-15) is traversed on the grounds that: "Neither of the Avruch et al. references teach that covalent modification of at least one of Ras or Raf binding fragments results in modulation of the binding and is required for the binding of Ras and Raf binding fragments."

26. It is the position of the examiner that Ras and Raf are binding partners and are first and

second polypeptides, one of which is immobilized (see '995, col. 13, lines 59-62 and col. 14, lines 13-22 (already formed complex)) and modification of the members in the complex is detectable (see col. 4, lines 52-59 antibody to Ras/Raf complex and not individual polypeptides), or the second polypeptide is labeled (see '995col. 13, lines 64-65). It is also the position of the examiner that Ras modifies Raf by phosphorylation or dephosphorylation (see '995 col. 4, lines 10-21), this being a species of the recited covalent modifiers that modulates binding. The modulation of binding is effected by a covalent modification, by phosphorylation or dephosphorylation which produces an active form or unactivated form of the binding partners (see'995, col. 6, lines 15-27).

27. The combination of claim limitations recited in claims17 and 41 are conditional claim limitations, specifically "is detectable", and need not be detectably labeled but must be able to be detected.

28. Claims 17 and 41 also recite "and covalent modification of at least one of the polypeptides results in modulation"; this is a future tense event defined by "results in".

29. Claims 17 and 41 list possible modifications, based upon the recited claim limitations, that can take place in the future that must be able to modify binding. Applicant's traversal is not commensurate in scope with the instantly claimed invention as now claimed. The rejection is maintained for reasons of record and responses set forth above Avruch et al (US Pat. 5,582,995) anticipates the instantly claimed invention which includes complexes that comprise Ras, Ras containing complexes that comprise first and second polypeptides immobilized on a support are disclosed in Avruch et al '995.

30. ***Rejection Maintained(Composition claims)*** The rejection of claims 17 and 41 under 35 U.S.C. 102(e) as being anticipated by Beach et al (effective filing date October 24, 1994) is traversed on the grounds that the covalent modification is required for binding which results in modulation of the binding of the first and second polypeptides.

31. It is the position of the examiner that the Raf/CDC25 complex comprises a covalent modification, the covalent modification being the transfer of a phosphate group (ATP) which results in phosphorylation (see col. 6, lines 15-29, col. 6, lines 56-61; col. 12, lines 55-60 (reaction mixture includes ATP). The addition of the covalent modification resulted in modulation of binding, specifically Raf kinase binds to CDC25 phosphatase through the addition of a phosphate group, a covalent modification, resulting in phosphorylation of CDC25 (see col. 9, lines 40-45).

32. Additionally, the combination of claim limitations recited in claims17 and 41 are conditional claim limitations, specifically "is detectable", and need not be detectably labeled but must be able to be detected. Claims 17 and 41 also recite "and covalent modification of at least one of the polypeptides results in modulation"; this is a future tense event defined by "results in". Claims 17 and 41 list possible modifications, based upon the recited claim limitations, that can take place in the future that must be able to modify binding. Applicant's traversal is not commensurate in scope with the instantly claimed invention as now claimed. Beach et al still discloses the instantly claimed invention directed to an immobilized polypeptide pair, the pair including the complex of Raf/CDC25, the pair comprising a covalent modification.

33. ***Rejection Maintained(Methods)*** The rejection of claims 18, 21-27 and 31 under 35 U.S.C. 102(e) as being anticipated by Beach et al (US Pat. 6,037,136, effective filing date October 24, 1994) is traversed on the grounds that Beach et al does not teach that covalent modifications of either CDC25 or Raf results in modulation of binding of CDC25 to Raf and

does not teach a covalently modified second binding partner polypeptide capable of associating with the first polypeptide.

34. Previously, the examiner cited col. 9, lines 40-45 of US Pat. 6,037,136 of Beach et al, that discloses binding of Raf to CDC25 is modulated by phosphorylation; without phosphylation, binding activity is reduced, but with the covalent modification by phophorylation, the association of the two polypeptides evidences activity. The disclosure of Beach et al still anticipates applicant's claimed invention as now claimed.

2. ***Maintained Double Patenting*** Claims 18,21-25, 34-35 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. US Pat. 6,656,696 is maintained for reasons of record as an effective terminal disclaimer was not submitted and the obviousness type double patenting rejection was not traversed on the record.

3. ***Maintained Double Patenting*** Claim 18 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. US Pat. 6,670,144 is maintained for reasons of record as an effective terminal disclaimer was not submitted and the obviousness type double patenting rejection was not traversed on the record.

4. ***Maintained Double Patenting*** Claims 18, 21-25, and 34-35 are is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. US Pat. 6,465,199 is maintained for reasons of record as an effective terminal disclaimer was not submitted and the obviousness type double patenting rejection was not traversed on the record.

5. ***Maintained Double Patenting*** Claims 21-30,34-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over allowed claims 1-2, 4-8, 10-14 of U.S. Patent Application 09/511,776 is maintained for reasons of record

as an effective terminal disclaimer was not submitted and the obviousness type double patenting rejection was not traversed on the record.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

35. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

36. 5736337,5763571,US005767075A US006573094B1 are cited to show methods of that screen for activity of immobilized first and second polypeptides that can be modified covalently.

37. Avruch et al (2001) is cited to show Ras activation of the Raf kinase.

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
April 28, 2006

L. F. Smith

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